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Controversial Issues Concerning Norepinephrine and Intensive Care Following Severe Traumatic Brain Injury

John F. Stover, Peter Steiger, Reto Stocker¹

Abstract

Norepinephrine and corresponding intra- and interorgan pathways are of clinical pathophysiologic and pharmacologic importance as exaggerated activation needs to be reduced and insufficient activation must be supported to prevent further deterioration and therapy-induced organ damage. This is of high relevance in critically ill patients in whom various norepinephrine-influenced organ systems are simultaneously affected with varying degrees of tolerability and resistance to norepinephrine-induced cell damage and finds its maximal challenge in patients suffering from severe traumatic brain injury (TBI). This comprehensive review describes complex pathophysiologic interactions, including hemodynamic, microcirculatory, hormonal, metabolic, inflammatory, and thrombocytic alterations overshadowed by differential consequences of commonly applied pharmacological interventions following TBI. Overall, investigations published to date suggest that receptor-dependent effects of norepinephrine might predispose to complex evolving deterioration especially during intensive care which is characterized by differentiated complication-driven changes and specific complication-dependent needs. In this context, thrombocytes and leukocytes with their adrenergic receptors and differential norepinephric functional regulation are ideal candidates to influence all organs at once. Despite its secure integration of norepinephrine in clinical routine, future emphasis must be directed at unmasking, monitoring, and controlling possible receptor-mediated detrimental influences which could offset anticipated organ protection.

Key Words

Catecholamines · Secondary injury · Monitoring · Critical care

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Introduction

An integral part of modern therapy aimed at preventing secondary injury following traumatic brain injury (TBI) is to maintain adequate cerebral perfusion. Elevating mean arterial blood pressure (MABP) and cerebral perfusion pressure (CPP) is achieved pharmacologically by continuously infusing vasopressors, e.g., norepinephrine. Experimental conditions following TBI mainly focus on early cerebral changes during short continuous norepinephrine infusion which does not necessarily reflect critically ill patients. As outlined in the schematic drawing (Figure 1) challenge to improve our understanding and thus ameliorate modern treatment modalities following TBI is to simultaneously consider the temporal profile of local and evolving systemic alterations with potential reciprocal influences which are simultaneously influenced by current therapeutic interventions. Although catecholamines are readily used in critically ill patients, differential organ-specific changes induced by catecholamines need to be considered and should be monitored to prevent affecting the anticipated neuroprotection. This comprehensive review focuses on pathophysiologically relevant inter- and intraorgan norepinephric pathways and characterizes various potentially harmful pharmaco-

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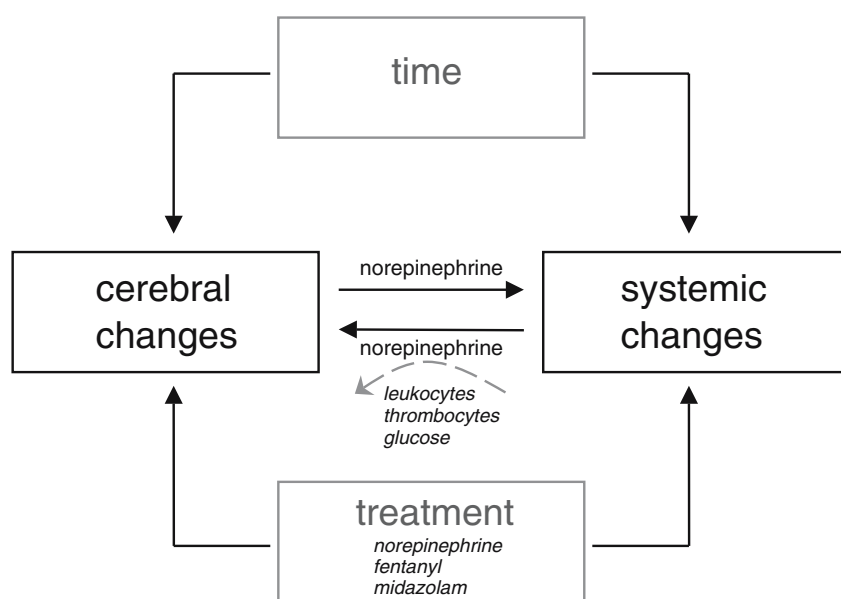


Figure 1. Schematic drawing depicting the principal pillars of simultaneous time-dependent pathophysiologic and pharmacologic changes which balance beneficial and disadvantageous norepinephrine-mediated actions. In critically ill patients, specific needs are dictated by characteristic changes over time, possibly requiring individual adjustment of interventions, making detailed monitoring indispensable.

dynamic effects of continuous norepinephrine infusion within the routine intensive care treatment of patients suffering from severe TBI.

Endogenous Release and Exogenous Norepinephrine Administration

Within minutes following a stressful event, activation of the hypothalamic–pituitary–adrenal axis amplifies release of norepinephrine, epinephrine, and cortisol from the adrenal gland [1]. These exhaustive alterations maintain hemodynamic stability, mobilize energetic reserves, influence the immune system, and adapt neuroendocrinological and hormonal alterations [1, 2]. Activation of the noradrenergic locus coeruleus stimulates various neuronal functional networks responsible for the increased level of alertness and sustained analgesia, and inhibits secretion of various hypothalamic and pituitary hormones, thereby suppressing reproductive, growth and thyroid functions [2]. The magnitude of this response reflects the extent of underlying injury and contributes to subsequent worsening if not controlled [3]. Under clinical conditions, norepinephrine is infused continuously together with volume resuscitation and hemorrhage/coagulation control to maintain defined blood pressure or CPP levels (Figure 2). In parallel, the sustained endogenous sympatho-autonomic activity is reduced by sedatives and analgetics.

Organ-Specific Effects of Norepinephrine

Extensive investigations of acute and chronic norepinephrine infusion have revealed important influences

on various organs which, among others, depend on administered dose, organ-specific receptor distribution, and binding availability of these receptors. Overall,

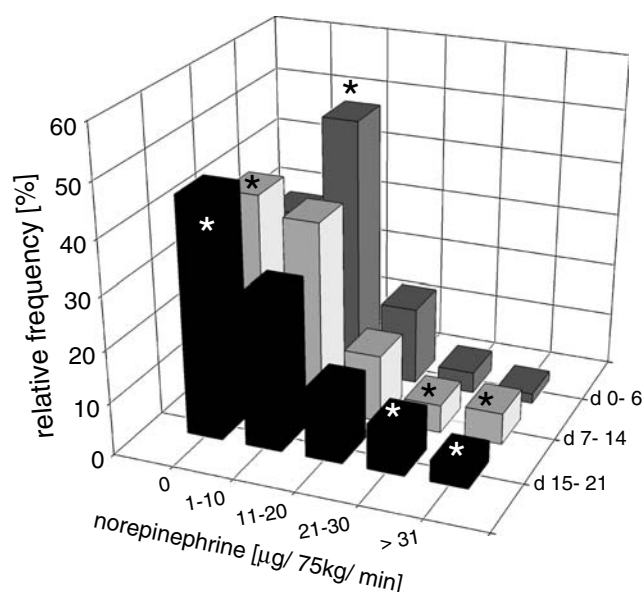


Figure 2. Relative frequency distribution of norepinephrine dose in 50 patients suffering from severe TBI up to 3 weeks following injury. Norepinephrine dose was adjusted to maintain CPP between 70 and 110 mmHg. During the first week predominant norepinephrine dose ranged from 1–10 µg/min. While the majority of patients stabilized, reflected by the sustained frequency without norepinephrine and the decreasing frequency within the norepinephrine dose ranging from 0.013–0.133 µg/kg/min, patients with a more difficult clinical course showed an increased frequency in high norepinephrine dose exceeding 21 µg/min (≥ 0.28 µg/kg/min) (* $p < 0.001$).

beneficial effects on individual organs may be offset by simultaneous alterations of other organ systems which demand following a 'brain-oriented' and avoiding a 'brain-centered' therapy. In this context, norepinephrine-driven improvement of cerebral perfusion and metabolism due to increased CPP occurs in face of reduced kidney, liver, and testis perfusion and metabolism [4]. The general concept of modern intensive care treatment is to guarantee adequate volume replacement and catecholamine administration within acceptable, i.e., organ-protecting limits. While increased volume administration allows to significantly reduce norepinephrine dosage [5], prevention of organ-endangering volume overload must be considered. Careful judgement of the individual situation is required to guide sequential or parallel administration of norepinephrine and fluids. In principal, single administration of high-dose norepinephrine in a patient in whom intravascular volume is depleted or reduced should be avoided as norepinephrine-mediated vasoconstriction will induce organ damage. A careful review of the literature produced only few clinical studies investigating the pharmacodynamic and pharmacokinetic profile of continuous norepinephrine infusion in healthy volunteers, nonseptic, and TBI patients. The majority of findings are derived from hemodynamically unstable patients suffering from sepsis and corresponding experimental sepsis models in various species. Given the facts that sepsis fulfills the same criteria of the systemic inflammatory response syndrome (SIRS) expanded by a bacterial infection and that SIRS can even develop in patients with isolated severe TBI [6], certain changes observed during these conditions might also be of relevance for the treatment of TBI patients, especially if sepsis develops. The complexity and diversity of posttraumatic intensive care involving various norepinephrine-influenced organs is depicted in the schematic drawing (Figure 3).

Heart, Circulation, and Macrohemodynamics

According to its characteristic receptor distribution, norepinephrine increases cardiac contractility (β_1) and peripheral resistance (α_1 receptors), thereby elevating systolic and diastolic blood pressure, increasing MABP, cardiac index, and total peripheral resistance (TPR) [7–11]. Pressure-dependently, coronary perfusion is improved in healthy animals [7]. However, norepinephrine might endanger cardiac viability as chronic administration of high-dose norepinephrine induces left ventricular hypertrophy [12–14] and may activate cardiotoxic cascades via stimulation of β_1 -adrenergic-driven apoptotic changes due to intracellular activation of Ca^{2+} -activated calmodulin kinase and release of free

oxygen radicals which is inhibited by β_2 stimulation [15]. It is important to keep in mind that improving MABP does not necessarily reflect ameliorated organ perfusion especially under pathological conditions [8, 10]. Despite normalized MABP, failure of improving impaired renal and mesenteric perfusion [8, 10] could reflect maintained autoregulation or insufficient increase in MABP due to massively disturbed autoregulation. This is also suggested by recent findings in septic patients in whom a further increase in MABP from 65 to 85 mmHg did not improve renal function [16].

Lungs

Apart from pressure- and volume-passive influences, norepinephrine interferes with pulmonary function by activating adrenergic receptors and stimulating the inflammatory response. Under experimental conditions, norepinephrine dose-dependently induces α_{1A} - and α_{1B} -adrenergic-mediated pulmonary vasoconstriction [17] which can be inhibited by fentanyl in vitro [18]. High-dose norepinephrine (0.1 mg/kg/h \approx 1.7 $\mu\text{g/kg/min}$, 128 $\mu\text{g/75 kg/min}$) continuously infused up to 72 h in healthy rats results in reversible pleural effusion and pulmonary venous congestion related to increased hydrostatic pressure [13]. The reversible left ventricular hypertrophy appears necessary to compensate and clear pleural effusion upon termination of norepinephrine infusion [13]. In addition, adrenergic-mediated inflammatory response with alveolar and interstitial edema formation contributes to functional and structural lung injury [14]. Under pathological conditions, the lungs are primed for sustained accumulation, activation, and sequestration of leukocytes [19] which could be aggravated by infused norepinephrine. Vasoconstriction in combination with increased leakage could impair preexisting regional perfusion/ventilation mismatch in intubated and ventilated ICU patients.

Intestines

α -adrenergic and β -adrenergic activation influences gut motility and intestinal functions. Splanchnic vasoconstriction shunts blood to heart, lungs, brain, and muscles. While epinephrine reduces intestinal and splanchnic perfusion leading to mucosa damage [20, 21], norepinephrine at 0.05 $\mu\text{g/kg/min}$ (\approx 3.75 $\mu\text{g/75 kg/min}$) is not associated with negative effects in animals and patients [8, 9, 22] as it does not impair intestinal perfusion and mucosal integrity despite a dose-dependent increase in splanchnic oxygen extraction [9]. Even under adverse conditions, as e.g. sepsis with or without ensuing shock high-dose norepinephrine at 0.18 or 0.45 $\mu\text{g/kg/min}$ is not harmful [20, 21]. Norepinephrine is superior to

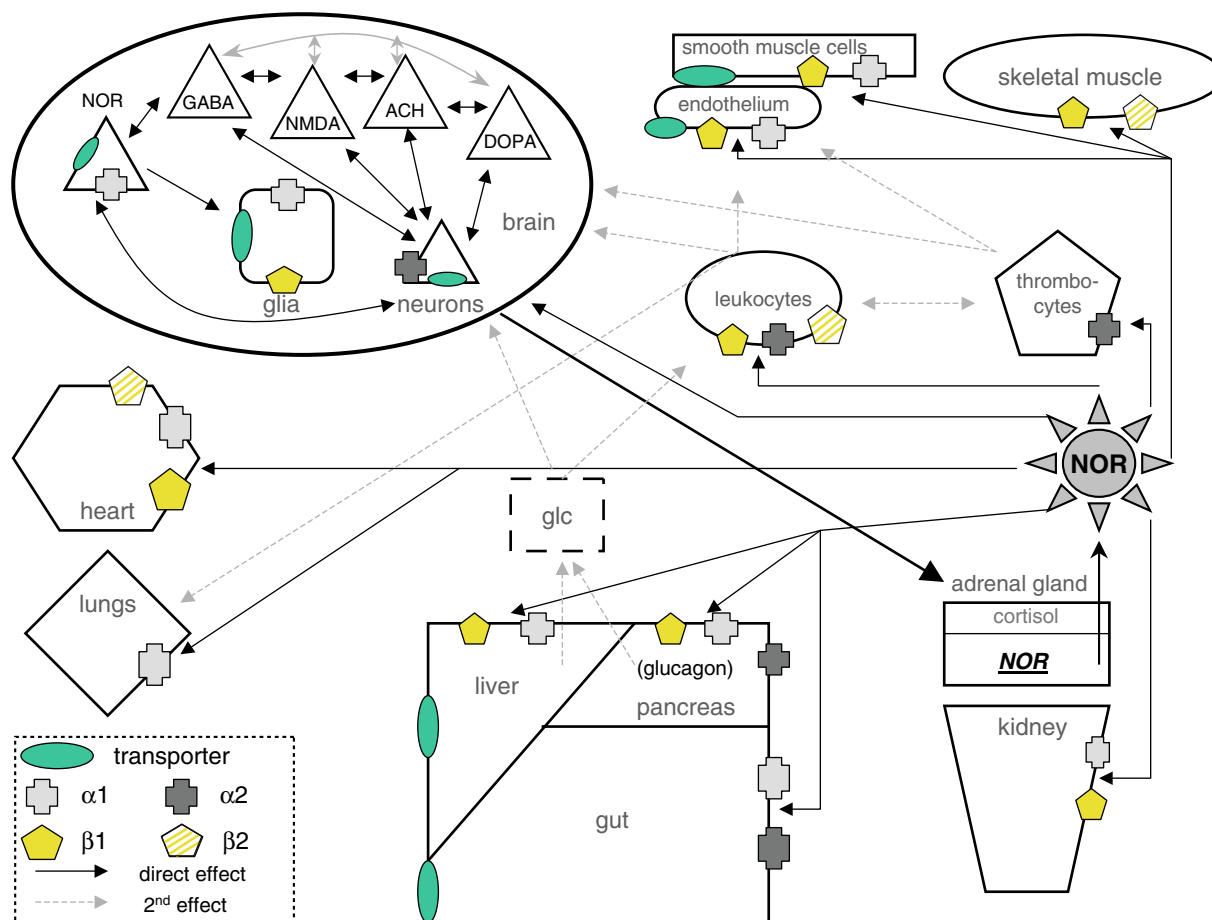


Figure 3. Schematic drawing of different organ systems with their complex intra- and interorgan influences involved in norepinephrine-mediated functional circuits. An unspecific stressful event stimulates adrenal release of norepinephrine which then receptor-dependently stimulates, inhibits, or disinhibits subsequent pathways with their own secondary cascades (specific details are given in the main text). Intravenously infused norepinephrine targets the same adrenergic receptors. The intact lines depict direct or primary norepinephrine-mediated effects; the broken lines show secondary effects involving leukocytes, thrombocytes, and elevated glucose levels, possibly inducing or aggravating cell damage (details are described in the main text).

phenylephrine, dopamine, vasopressin, and epinephrine by improving splanchnic perfusion, oxygen delivery, and lactate uptake [23–26].

Kidneys

The strong oxygen dependency and low critical threshold for oxygen consumption in combination with the required high renal perfusion pressure (kidney: 80–180 mmHg vs. liver: 50–150 mmHg) make the kidneys highly vulnerable to impaired perfusion and oxygen supply [27, 28]. Apart from volume administration, norepinephrine is beneficial, especially in face of nitric oxide (NO)-mediated vasodilation and disease-related vasoparalysis which disturbs various modulators (catecholamines, NO, angiotensin II, vasopressin, and endothelin-1) and intracellular pathways [29]. Despite

norepinephrine-induced reduction in renal perfusion observed in healthy volunteers at $0.118 \pm 0.03 \mu\text{g/kg/min}$ [30], norepinephrine pressure-dependently elevates renal perfusion, increases urine output and creatinine clearance in healthy [7, 31] and septic animals [31]. Adverse effects were ruled out in a retrospective study including 200 cardiac surgery patients in whom norepinephrine infusion did not increase serum creatinine levels [32]. Under experimental and clinical septic conditions norepinephrine required to elevate MABP to 70 mmHg needs to be increased severalfold [31, 11], reaching values as high as $1.3 \pm 0.3 \mu\text{g/kg/min}$ ($\approx 97.5 \pm 22.5 \mu\text{g/75 kg/min}$) in humans [11] or 3.1 ± 0.3 versus $0.2\text{--}1 \mu\text{g/kg/min}$ ($\approx 232.5 \pm 22.5 \mu\text{g/75 kg/min}$ vs. $15\text{--}75 \mu\text{g/75 kg/min}$) in septic versus control rats [8]. While increasing MABP in nonseptic patients does not alter renal

function [11, 32], suggesting intact autoregulation, elevating MABP from 51 ± 3 to 79 ± 7 mmHg in septic patients significantly increases urine flow and creatinine clearance [11]. This, however, is contrasted by the recently published findings that an increase in MABP from 65 to 85 mmHg does not improve renal function in septic patients [16]. Filtration and resorption processes are under adrenergic influence: renal vasoconstriction in conjunction with stimulated β_1 secretion of renin with subsequent activation of the vasoconstrictor angiotensin II and release of aldosterone results in decreased glomerular filtration and increased retention of sodium, reducing loss of fluid via urine. In addition, norepinephrine decreases tubular sodium secretion.

Metabolism

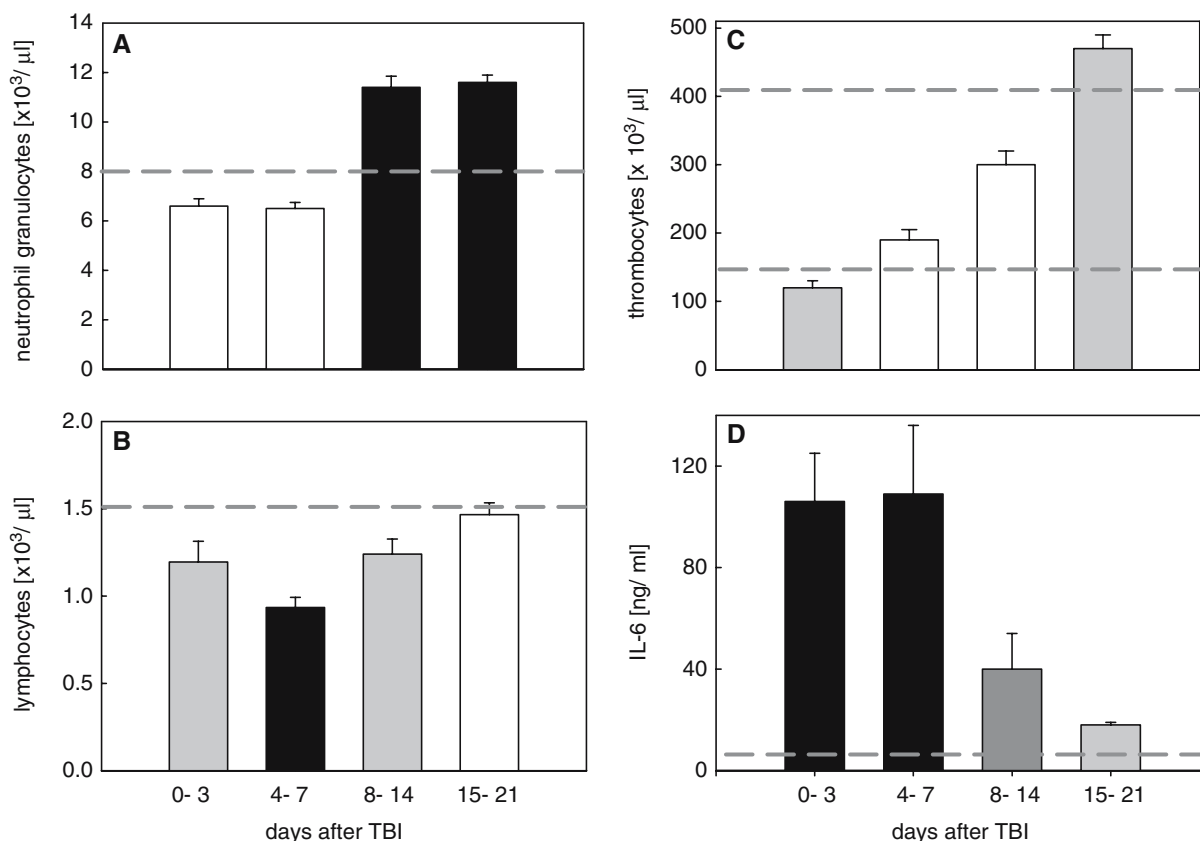
Complex Regulation of Lipolysis, Proteolysis, Glycolysis, and Glycogenolysis

Catecholamines differentially influence actions of insulin and glucagon, hormones which control fat, protein, and glucose metabolism. In critically ill patients, sustained release of proinflammatory and catabolism-aggravating cytokines [33] occurs in face of disturbed hormonal regulation, impaired nutrient uptake, and sustained metabolism. Lipolysis mediated by activation of α_2 and β_1 -adrenergic receptors and regulated at the level of cAMP production by different intracellular cascades releases free fatty acids and glycerol and produces free oxygen radicals [34, 35]. Proteolysis is not only restricted to injured muscle due to activation of the ubiquitin/proteasome system, calcium- and calpain-dependent release of myofilaments from the sarcomere and upregulation of macrophage-associated lysosomal proteolysis [36, 37], but involves all muscles as observed clinically by the generalized muscle loss in critically ill patients without any obvious muscle trauma. Thus, norepinephrine by itself or in conjunction with glucocorticoids, cytokines, and altered insulin responsiveness with inadequate amino acid supply can induce myofibrillary breakdown and insufficient synthesis [38, 39]. Sustained ATP and oxygen consumption of β -adrenergic-stimulated muscular $\text{Na}^+\text{--K}^+\text{--ATPase}$ could contribute to muscle degradation. Norepinephrine-induced proteolysis [40] has been challenged by recent reports suggesting anabolic effects via stimulation of β_2 - and β_3 -adrenergic receptors in rats [41]. For the complex regulation of glucose metabolism, activation of α_2 -adrenergic receptors inhibits insulin secretion, thus elevating blood glucose levels due to attenuated uptake in myocytes and lipocytes while stimulation of α_1 - and β -adrenergic receptors increases pancreatic release of insulin which decreases blood glucose due to increased cellular

uptake and intracellular degradation [42]. During critical care with disturbed peripheral glucose uptake and metabolism [43], the predominant α_1 -adrenergic stimulation with sustained hepatic gluconeogenesis and glycogenolysis will increase blood glucose levels during high-dose norepinephrine infusion [21, 44]. In addition, pancreatic glucagon release stimulated by α_1 , α_2 , and β receptors increases blood glucose [45, 46]. In healthy volunteers, norepinephrine at 0.1 $\mu\text{g/kg/min}$ significantly increases glucose production and uptake [47]. In patients, norepinephrine at 0.18 or 0.45 $\mu\text{g/kg/min}$ [21] elevates blood glucose ≥ 10 mM (180 mg/dl) which aggravates underlying brain damage and impairs survival [48] due to local acidosis and sustained cerebral inflammatory response. Thus, increased insulin administration might become inevitable whenever high-dose norepinephrine is required to maintain certain MABP and CPP levels.

Oxidative Metabolism and Organ Energetics

As observed in healthy volunteers, norepinephrine dose-dependently increases whole body oxygen consumption between 0.06 and 0.2 $\mu\text{g/kg/min}$ which could contribute to adverse effects in critically ill patients [49] despite increasing oxygen delivery, especially with underlying disturbed cell function. Under clinical conditions, the use of more invasive procedures, including pulmonary artery catheter, transjugular cannulation of the hepatic vein, assessment of hepatic indocyanine-green clearance, endoluminal positioning of a tonometric gastric tube and laser Doppler catheters allows to determine cardiac index, hepatosplanchnic oxygen extraction, lactate production, alanine uptake, and blood flow, gastric mucosal pCO_2 production, and jejunal mucosal perfusion, respectively [9, 21]. In septic patients, norepinephrine significantly increases splanchnic oxygen and lactate extraction. Elevated lactate predominantly results from β -adrenergic-stimulated muscular $\text{Na}^+\text{--K}^+\text{--ATPase}$ which is then oxidized by hepatic gluconeogenesis (Cori cycle). These effects are mainly mediated by epinephrine [50] or high-dose norepinephrine. The dose-dependent increase in splanchnic oxygen extraction especially in patients with low baseline cardiac index values < 2.4 l/min/ m^2 suggests that intravascular volume depletion had not been restored [9]. Under experimental conditions, parameters of organ energetics as e.g., ATP, phosphocreatinine, and lactate/pyruvate ratio determined in the muscle, liver, gut, kidney, and heart, as well as humoral arterial parameters (glucose, lactate, lactate/pyruvate ratio, ketone body ratio) are not altered by norepinephrine at 0.2 $\mu\text{g/kg/min}$ in otherwise healthy rats [8].



Figures 4a to 4d. Temporal profile of changes in neutrophils (a), lymphocytes (b) thrombocytes (c) and IL-6 (d) determined in 20 patients with severe TBI up to 3 weeks following injury. The dashed lines reflect upper (neutrophils, IL-6) or lower normal limits (lymphocytes, thrombocytes). Color-coded bars reflect the degree of pathological deviation from normal values (black: strong; dark grey: moderate; light grey: mild; white: normal).

Inflammatory response

Complex Alterations Contributing to Cellular Dysfunction

The inflammatory response comprises a plethora of complex cellular and humoral alterations which support local inflammation aimed at confining existing tissue damage by concomitantly inhibiting systemic inflammation to prevent uncontrollable damage of other primarily uninjured organs. However, this fine-tuning is disturbed in critically ill patients, resulting in SIRS [6]. TBI induces local and systemic inflammation as evidenced by an upregulation of intestinal NF- κ B, ICAM-1, TNF- α , and IL-6 [51, 52].

Differential Influence of Norepinephrine

Initially, β_2 -adrenergic activation increases circulating lymphocytes derived from the marginal pool and the spleen, while α -adrenergic activation subsequently elevates circulating neutrophil granulocytes released from the marginal pool and the lungs [53] due to reduced adhesion to vascular endothelium [54]. Subsequently,

lymphopenia with a mismatch between T helper and T cytotoxic lymphocytes with sustained neutrophil activity [55] develops. Released proinflammatory cytokines, in turn, can influence central noradrenergic pathways [56]. Overall, norepinephrine interferes with immunocompetence [57] which could contribute to evolving multiorgan failure [58] (Figures 4a, 4b, and 4d). Norepinephrine induces apoptosis, impairs mitochondrial membrane potential in lymphocytes and natural killer (NK) cells [59], inhibits cytokine secretion, target binding, and programming for cytotoxicity in NK cells [60] and suppresses phagocytosis, generation of oxygen radicals, and neutrophilic and lymphocytic chemotaxis during prolonged adrenergic stimulation [61, 63]. In addition, norepinephrine dose-dependently inhibits oxygen consumption in nonstimulated human peripheral blood mononuclear cells, while in activated cells β -adrenergic receptors are desensitized and α -adrenergic receptors are sensitized, resulting in sustained norepinephrine-mediated stimulation of oxygen consumption [62]. Dendritic cells important in fine-tuning

the appropriate immune response to invading pathogens and tolerance to self-antigens are under differential β -adrenergic control [64]. In addition, β -adrenergic activation controls release of pro- and antiinflammatory cytokines [44, 65, 66] and contributes to depressed cell-mediated inflammation by stimulating the peroxisome proliferator-activated receptor gamma (PPAR γ), a nuclear hormone receptor that mediates antiinflammatory actions [67], as well as inhibiting NF- κ B and activating I- κ B α [68, 69]. At low norepinephrine concentrations (≈ 20 nM), α_2 receptor activation stimulates TNF- α and IL-1 β production in hepatic Kupffer cells which is inhibited by high concentrations via β_2 -adrenergic receptors [56]. β_2 -adrenergic stimulation also induces cellular immunosuppression by downregulating various receptors on stimulated human peripheral blood mononuclear cells [70]. A loss in endogenous norepinephrine appears crucial in inducing, maintaining, and impairing resolution of brain inflammation [71].

Thrombocytes

Physiological Control of Organ Function

Thrombocytes are crucial in functionally interlocking coagulation with the innate immune system [72]. Apart from stopping hemorrhage by receptor-mediated (P-Selectin) adherence to endothelial cells, leukocytes, and other thrombocytes [73], thrombocytes activate the coagulation cascade and release a multitude of different mediators which also control vascular tone, e.g., serotonin, norepinephrine, thrombin, prostacyclin, histamine, and bradykinin. Thrombocytes restrict local tissue injury, recruit and activate neutrophils through the release of IL-8 [61], enable leukocyte tissue penetration and further thrombocyte aggregation via release of matrix-degrading metalloproteinases [74]. The functional complexity is reflected by the plethora of intracellular pathways [75], and the involvement of cytokines (TNF- α) and endothelial cells (NO) within the regulation of thrombus formation [76].

Pathological Response

Exaggerated local thrombocyte-leukocyte activation can impair microvascular blood flow [77, 78] and compromise thrombocyte-mediated stabilization of endothelial cells and protection against oxidative tissue injury [79] as increased neutrophil activation and induced endothelial damage result in a burst of free radicals and release of digestive enzymes also observed in thrombocytopenic patients suffering from multiorgan disease [80]. P-Selectin-activated pathways promoting leukocyte and thrombocyte adhesion contribute to post-traumatic brain edema formation in knock-out mice

[81]. Released thrombin exerts neurotoxic effects, impairs memory functions, and decreases cerebral perfusion under experimental conditions [82] which is inhibited pharmacologically [83]. Following severe injury, elective orthopedic surgery or vascular graft insertion, thrombocytes are in a state of increased activation as judged by expression of surface proteins, release of soluble adhesion molecules [84–89], hyperaggregation, and sustained adhesiveness [90–92].

Noradrenergic Influence

Formation of thrombocyte-neutrophil aggregates as well as receptor expression on thrombocytes and neutrophils are increased through α -adrenergic stimulation [93], possibly aggravating disease-related changes. α_2 -adrenergic stimulation activates intracellular cascades and dose-dependently promotes thrombocyte activation [94, 95] which is inhibited pharmacologically [94, 96, 97]. Sustained norepinephrine-stimulated activation with subsequent consumption and peripheral sequestration of thrombocyte-bound leukocytes can decrease circulating thrombocytes and contribute to multiorgan failure [85, 98, 99] (Figure 4c).

Brain

Transmitter and Local Functional Circuits

The excitatory neurotransmitter norepinephrine originates in the locus coeruleus and lateral tegmental nuclei of the brain stem from where it activates different diencephalic and telencephalic regions, modulates cortical neuronal activity, induces arousal and alertness, enables memory formation, consolidation, reinforcement, and information retrieval [100–109] by influencing hippocampal input [110]. Norepinephrine also modulates hormone release from pineal gland [111], pituitary [112–114], and hypothalamus [115], influences processing of arterial chemoreceptor afferent inputs [116], coordinates respiratory pacemaker and nonpacemaker neurons [117], and controls the esophageal-gastric relaxation reflex [118] by α -adrenergic receptors. Age-related reduction in cortical noradrenergic neurotransmission affects spatial learning and memory performance [119]. Norepinephrine exerts anti- and prooxidative functions on various isolated neurons [120–122]. As all transmitters, norepinephrine not only influences neuronal and glial function but is also subject to site-dependent regulatory influences by other transmitters: norepinephrine stimulates glial release of ATP which regulates postsynaptic efficacy of glutamatergic neurons [123]; activation of presynaptic cholinergic receptors facilitates noradrenergic transmission [124]; stimulation of presynaptic GABA $_A$ receptors on glutamatergic

neurons within the locus coeruleus contributes to the excitability and activity of noradrenergic neurons due to functional disinhibition [125]; noradrenergic stimulation of basal ganglia and cortical glutamatergic neurons can be inhibitory (α_2) [126, 127] or excitatory (β_1) [126]; activation of α_1 receptors inhibits dopamine release in midbrain neurons [128] but induces dopamine release in the medial prefrontal cortex [129]; hippo-campal and cortical norepinephrine release are under glutamatergic and dopaminergic influence [129, 130]; α_2 -adrenergic presynaptic activation diminishes norepinephrine release and reduces the inhibitory action of GABA-ergic inputs in brainstem neurons, thereby disinhibiting histaminergic neurons [131]; glial glutamate uptake is mediated by α_1 -adrenergic stimulation and inhibited by β -adrenergic activation [132].

Vasoregulation

Apart from static, myogenic, and metabolic influences, including various circulating and local endothelial mediators, norepinephrine modulates proximal, large diameter segments of cerebral arteries and arterioles (10–20 μ m). The resulting local vasodilation and vasoconstriction assures constancy of cerebral perfusion with MABP values ranging from 50–170 mmHg. Endogenous norepinephrine released from adrenergic neurons in close apposition to vessels and glia [133] stimulates Ca^{2+} -mediated astrocytic-driven vasoconstriction [134], and activates β_2 receptors on nitrergic nerve terminals, thereby releasing vasodilating NO while co-localized α_2 receptors inhibit NO release and mediate vasoconstriction [135]. Exogenous norepinephrine primarily targets endothelial α - and β -adrenergic receptors as the BBB with its enzymes [136] and specific transporter localization inhibits free norepinephrine penetration [137]. However, α -adrenergic-induced endothelial permeability enables uncontrolled passage with subsequent neuronal and glial activation [138].

Metabolism

In addition to its effect on glial glycogenolysis and glycolysis [139], glycogen synthesis [140, 141], and glutamine uptake [142], norepinephrine increases lactate uptake in cultured mouse cortical neurons [143] to assure sufficient energy transfer from astrocytes to neurons under conditions of increased energetic demand.

Glucose-Dependent Changes

Hypoglycemia activates central counter-regulatory processes to correct low blood-glucose levels and avoid brain damage. In this context, glutamatergic stimulation of the sympathoadrenal and hypothalamic-pituitary

adrenal axis [144], and release of norepinephrine within the ventromedial hypothalamus result in central α_2 - and β -adrenergic activation [145] and adrenal secretion of counter-regulatory hormones [146].

Plasticity and regeneration

Within the functional and structural complexity of the brain, various transmitters including norepinephrine receptor-dependently modulate excitability and modify neuronal threshold for activity-dependent synaptic changes which influence cortical plasticity [147], prolong survival of cultured human neuroblastoma cells, induce neuronal differentiation, and influence synaptic connectivity [148]. Further evidence supporting norepinephrine-mediated regeneration is found in the facts that noradrenergic depletion increases cerebral inflammation [149] and that administration of clonidine, which selectively reduces α_2 -mediated synaptic norepinephrine release and reduces plasma catecholamine levels [150], impairs posttraumatic functional recovery and even reinstates neurological deficits [151, 103].

Norepinephrine and Traumatic Brain Injury

Following TBI, norepinephrine is of clinical interest for several reasons: (1) disturbed cerebral noradrenergic circuits contribute to evolving brain damage; (2) these changes give rise to potential pharmacological targets ameliorating neuropsychological and cognitive disturbances; and (3) infused norepinephrine is used to improve reduced cerebral perfusion following TBI.

Posttraumatic Changes in Brain Norepinephrine and Potential for Pharmacologic Regeneration *Cerebral Functional and Structural Disturbances*

Following an initial transient increase, norepinephrine turnover is depressed in TBI rats [152, 153] which together with reduced axonal transport and decreased brain norepinephrine amount induces behavioral and psychological abnormalities [154]. Furthermore, disturbed noradrenergic circuits upregulate potentially harmful excitatory pathways [152] and constrict isolated rat middle cerebral artery [155] and posttraumatic pial arterioles [156], inducing injury-aggravating cerebral ischemia.

Differential Pharmacological Targets

The initial sustained clearance of norepinephrine from the extracellular space is thought to be autoprotective and should not be influenced pharmacologically as this promotes edema formation [153]. The subsequently depressed norepinephrine turnover, however, should be targeted to support noradrenergic influence on regen-

eration, plasticity, behavioral, and cognitive improvement [157–159]. In this context, α_1 and β_1 -adrenergic antagonists (prazosin; propranolol) and α_2 -adrenergic agonists (clonidine) should not be given, as these drugs impair cognitive functions [160] and reinstate neurological deficits [151, 161] without worsening or inducing histological damage. This is in sharp contrast to the differential pharmacologic interventions used within the LUND concept, an ICP-oriented, low CPP-controlled and volume-guided treatment paradigm, where clonidine and metoprolol together with low-dose thio-pental and continuous fentanyl and midazolam infusion are used [162]. Posttraumatic disturbance of the noradrenergic system shares certain similarities with pathophysiological alterations involved in depression and Parkinson's disease. Thus, norepinephrine, mixed serotonin/norepinephrine, and dopamine/norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, amphetamines (norepinephrine release and inhibited uptake), amantadine and memantine (NMDA receptor antagonists with dopamine release), L-DOPA (norepinephrine precursor), and bromocriptine (dopamine agonist) used to treat these chronic neurodegenerative diseases have been in focus to ameliorate posttraumatic psychomnestic deficits [163]. First clinical trials with small patient numbers showed promising results in treating posttraumatic depression and improving cognitive functions following administration of milnacipran, desipramine, or amantadine [164–166]. Based on experimental data in non-TBI rats, additional α_2 -adrenergic inhibition to increase extracellular norepinephrine [167] as well as repetitive administration are required to induce beneficial effects, since antidepressants usually need 2–3 weeks of chronic administration before cellular and clinical alterations are detected [168, 169]. Unfortunately, psychostimulative antidepressants carry side effects [163] and may also impair memory consolidation [170]. Modulating α -adrenergic changes may be age- or model-dependent [171] which makes a simple transfer from bench-to-bed difficult. Prospective controlled studies are required to evaluate the beneficial effects of adjuvant neuropsychopharmacotherapy started early after TBI, i.e., before patients are transferred to neurorehabilitation centers.

Posttraumatic Changes in Cerebral Perfusion and Metabolism

Secondary Damage

In principal, severe TBI is characterized by a primary lesion which can be worsened during its clinical course owing to secondary injuries [172] – e.g., insufficient cerebral perfusion which is considered a treatable and avoidable event.

Regional and Temporal Heterogeneity

Observational studies reveal regional and temporal heterogeneous changes in perfusion (hypoperfusion, vasospasm, and hyperemia) [173], metabolism (hypo- and hypermetabolism [174] with enzymatic disturbances [175]), and vascular reactivity [176]. Norepinephrine can influence these alterations. This regional and temporal heterogeneity conveys to pharmacologically targeted perfusion deficits, which, in turn, requires intensified monitoring to avoid exaggerated and insufficient treatment. In this context, experimentally elevating MABP and CPP at 24 h after TBI, when pericontusional perfusion normalizes, induces hyperemia [177]. Hyperemia, a sign of impaired cerebral autoregulation [178], elevates ICP and could aggravate brain damage via norepinephrine-induced increase in hydrostatic pressure or receptor-mediated activation of detrimental cellular changes.

Norepinephrine-Induced Increase in MABP, Cerebral Perfusion and Metabolism

Apart from the endogenous increase in metabolism-driven cerebral perfusion [179], norepinephrine dose-dependently increases MABP which – depending on the investigated species and the induced level of arterial hypertension [155] – increases cerebral blood flow (CBF) and metabolism [180, 181], has no effect [182], increases CBF without influencing glucose metabolism [155] or even decreases CBF [183, 184]. With a structurally injured or functionally impaired BBB encountered following TBI [185] and induced by norepinephrine [184], respectively, infused norepinephrine can penetrate the brain [186] and increase CBF via β -adrenergic activation of glial and neuronal activity [181, 183]. Norepinephrine-induced increase in cerebral perfusion also improves cerebral oxygenation in rats [177, 187] and patients [188–190]. The pressure-dependent increase in cerebral perfusion is also related to widening of spastic cortical arterioles and flushing of vessels with microthrombosis as revealed by in vivo intravital microscopy in TBI rats [177]. Contrary to experimental conditions, the norepinephrine-ameliorated cerebral perfusion and reduction in ischemic brain volume in patients was not associated with increased cerebral metabolism, possibly related to the concomitant administration of sedatives and analgetics. In fact, cerebral oxygen consumption was significantly reduced, possibly related to increased inflow of sedatives and analgetics or reversal of ischemic changes due to improved perfusion [191]. As observed under experimental conditions, norepinephrine-induced regional alterations might contribute to prolonged increase in CBF [187], related to locally released vasoactive mediators – e.g., NO and augmented

cellular activity. Sustained NO production due to increased glutamate-mediated neuronal activity induces cGMP-dependent smooth muscle relaxation resulting in vasodilation and increased perfusion to meet metabolic demands. In addition, catecholamines could contribute to vasodilation by scavenging free radicals [119] which have been shown to inactivate NO [192]. The significant increase in extracellular pericontusional glutamate concentrations related to β -mediated reduced glial glutamate uptake [131], sustained neuronal release, and facilitated penetration via a damaged BBB could explain the increased cortical EEG activity [187]. Alternatively, elevated EEG power could reflect preserved neuronal integrity due to improved tissue perfusion and oxygenation.

Increased Posttraumatic Brain Damage

To avoid additional posttraumatic ischemic damage, MABP and the calculated CPP are increased and maintained ≥ 70 mmHg which prevents an increase in cortical contusion volume in TBI rats [193]. However, experimental and clinical studies clearly show that CPP values ≥ 90 mmHg are indispensable to increase and normalize local cerebral perfusion [177, 187, 191]. Consequently, higher norepinephrine amounts are required. This, in turn, could increase the risk for additional norepinephrine-dependent alterations – e.g., sustained pericontusional hemorrhage [194]. While low-dose norepinephrine (0.15 $\mu\text{g/kg/min}$) significantly reduced cortical contusion volume, higher dose (0.3 and 1.0 $\mu\text{g/kg/min}$) did not influence contusion compared to control rats. Pericontusional hemorrhage was significantly increased at all doses, being mostly pronounced at 0.3 and 1.0 $\mu\text{g/kg/min}$. To limit potential detrimental side effects, CPP should not exceed 120 mmHg which significantly increased cortical contusion volume in rats [193]. In TBI patients, CPP values between 100 and 120 mmHg appeared safe as they did not induce intracranial hypertension in patients with or without vasopressors [195]. It remains to be determined if these adverse effects are caused by elevated hydrostatic pressure due to increased TPR or related to direct, possibly additive norepinephrine-induced pharmacodynamic influences. In cases of intracranial hypertension as investigated experimentally by increasing intracranial volume inflating a balloon [196] or infusing fluid into the cisterna magna [197] cerebral perfusion is impaired and the upper limit of CBF autoregulation is reduced, respectively. Thus, the ICP-dependent narrowing of the cerebral autoregulation interval might increase the risk for norepinephrine-mediated brain injury, as higher norepinephrine dose is required to elevate CPP. Then

again, impaired cerebral perfusion might prevent its penetration, thereby reducing the risk of norepinephrine-mediated cell damage.

Traumatic Brain Injury, Norepinephrine, and Inter-Organ Changes

Pharmacokinetics

Plasma norepinephrine is influenced by organ dysfunction. While continuous norepinephrine infusion dose-dependently increases plasma levels [198] in nonseptic TBI patients, septic patients show a significant decrease in norepinephrine clearance resulting in prolonged half-life [199]. This, in turn, could aggravate adrenergic organ damage. To properly control administration of drugs in the critically ill, changes in volume of distribution, elimination half-life, protein binding, clearance, and active metabolites need to be considered on an individual and daily basis to determine the appropriate dose and possibly attenuate developing tolerance [200] and also improve treatment of withdrawal symptoms [201].

Inflammation- and sepsis-mediated encephalopathy

This area comprises a plethora of complex pathophysiological alterations related to microorganisms and their toxins, inflammatory mediators, metabolic disturbances, changes in cerebral perfusion, alterations in amino acid and neurotransmitter homeostasis, and aggravated energy expenditure [202]. In otherwise healthy rats, systemic endotoxemia induces cerebral inflammation [203, 204] but fails to influence cerebral perfusion [205]. In brain-injured rats, sustained systemic inflammation significantly impairs cerebral vascular and metabolic response [206] and aggravates TBI-induced local inflammation [207]. Under these conditions, norepinephrine is of importance as the increased cerebral oxygen consumption and cerebral perfusion are mediated by β -adrenergic activation [208], cerebral norepinephrine uptake and synthesis is impaired [209, 210], and central (brain) as well as peripheral (thrombocytes) α_2 -adrenergic transmission is disturbed [211]. While norepinephrine infusion does not adversely affect cerebral perfusion in endotoxemic sheep [212], similar investigations have not yet been performed following TBI with severe inflammation.

Receptor Regulation

Chronic receptor stimulation or inhibition alters receptor affinity and activity due to phosphorylation, posttranscriptional, and posttranslational changes. In this context, prolonged endogenous as well as exogenous catecholamine administration reduces α_2 receptor affinity in human thrombocytes [95] and rat brain [213],

and decreases β_2 receptors in human mononuclear leukocytes [214] which might be influenced by certain genetic predisposition to differential β_2 adrenergic receptor regulation as seen in human lymphocytes [215] and human neutrophils [216]. In critically ill patients, β -adrenergic receptors of circulating lymphocytes are reduced [217] and inflammatory cytokines might impair β -adrenergic receptor-dependent production of the regulatory cAMP [217]. Adrenergic receptors are also influenced by steroids, retinoids, and thyroid hormones at the level of transcription, resulting in a decreased expression of adrenergic receptors in critically ill patients with disturbed hormonal influence. Ensuing arterial hypotension requires steroid substitution to increase sensitivity to α_1 receptor stimulation [218].

Influence of Opioids and Benzodiazepines

Basic treatment of patients suffering from severe TBI includes continuous intravenous infusion of opioids (e.g., fentanyl) and benzodiazepines (e.g., midazolam). Apart from sedation and analgesia, opioids and benzodiazepines can induce tolerance, predispose to withdrawal symptoms, influence thrombocyte and leukocyte functions, and modulate adrenergic responsiveness of smooth muscle cells. Midazolam inhibits norepinephrine release from sympathetic synapses [219] and allosterically modulates α -adrenergic receptors of smooth muscle cells [219, 220]. Midazolam dose-dependently inhibits activation of human thrombocytes [221, 222], reduces thrombocyte-leukocyte interactions [221], inhibits neutrophil apoptosis and monocyte chemotaxis [223, 224], thereby influencing the inflammatory response. Chronic administration of fentanyl inhibits dobutamine-related hemodynamic changes by modulating β -adrenergic receptors [225] and reduces α_1 pulmonary vasoconstriction [18]. In addition, chronic opioids promote astrogliosis which is reduced by α_2 inhibition [226]. Immunosuppressive properties of opioids [227] and α_2 -mediated thrombocyte activation are discussed controversially [228–230].

Withdrawal Symptoms

Chronic opioid and benzodiazepine infusion changes function of opioid and adrenergic receptors, thereby promoting drug dependence and disturbed arousal. Ensuing withdrawal symptoms can be modulated pharmacologically by α_2 -adrenergic agonists and α_1 and α_2 antagonists to suppress excessive norepinephrine release [231] and activation of the hypothalamus–pituitary–adrenocortical axis [232]. Pharmacological control of withdrawal symptoms, however, is complex as α_2 inhibition (yohimbine) preceeding α_2 stimulation

(clonidine) is superior to pretreatment using yohimbine or clonidine alone [233, 234]. Under clinical conditions, opioids and benzodiazepines should be reduced slowly [201]. Arising “sympathetic storm”, characterized by hypertension, tachycardia, tachypnea, arousal without adequate responsiveness, sweating, and increased energy expenditure [235] usually requires further sedation. While clonidine is commonly used, newer data suggest its avoidance. An internationally valid concept of which agents to use and how to proceed is still lacking and is strongly needed to avoid interfering with anticipated neuroprotection.

Open Questions for Future Clinical and Experimental Research

Despite its daily use, relatively few data is available related to time-dependent differential influences of norepinephrine-induced and receptor-mediated organ-specific alterations in critically ill patients suffering from severe TBI with and without additional organ dysfunction. To improve current treatment modalities, future research is warranted to address specific questions.

1. Pharmacokinetics and pharmacodynamics

- Is there a characteristic temporal profile for critically ill patients?
- Are there differences in complicated (SIRS/ sepsis) vs. noncomplicated cases?
- Do these changes correlate with systemic and local monitoring parameters?
- Can changes within the injured brain be assessed by calculating arterio-jugularvenous differences?

2. Systemic and local monitoring

- Which parameters should be integrated in daily clinical routine?
- How many measurements are required?
- Will changes reflect evolving impairment or completed perturbation?

3. Detrimental effects of infused norepinephrine

- Are potential adverse effects dependent on dose or length of administration?
- Is activation of thrombocytes and modulation of leukocytes really induced by infused norepinephrine or a mere *in vitro* effect?
- Does infused norepinephrine promote brain contusion growth and hemorrhage?

4. Disturbed vascular reactivity and autoregulation

- Does norepinephrine infusion increase the risk of cell damage in case of disturbed vascular reactivity and autoregulation?

- Should other vasoconstricting agents be used when testing autoregulation?
 - Is pretreatment with β -blockers essential to prevent impairment of cerebral metabolism upon increasing norepinephrine dose?
5. Induced dependence, tolerance, and withdrawal
 - How should drug dosage be reduced to avoid a surge in norepinephrine release?
 - Is this sustained noradrenergic response detrimental?
 - Does clonidine administration impair anticipated neuroprotection and affect neurorehabilitation processes?
 - Which pharmacological paradigm should be followed to replace clonidine?
 6. Pharmacological promotion of norepinephrine-dependent regeneration
 - Can plasticity, regeneration, and neuropsychomestic deficits be influenced in patients with severe TBI?
 - Which pharmacological compounds should be used?
 - When should administration of these drugs start?
 7. Change in therapeutic strategy
 - Will an increase in cerebral metabolism depressing drugs reduce the required norepinephrine dose and thus decrease potential adverse side effects?
 - Will this relate to an improved clinical course and subsequent neurorehabilitation?

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